INTERNATIONAL INSTITUTE OF SYNTHETIC RUBBER PRODUCERS, INC.

June 24, 1998

Dr. C. W. Jameson
ETP/NIEHS
National Institute of Health
P.O. Box 12233
Research Triangle Park, North Carolina 27709

Dear Dr. Jameson:

SUBJECT: Comments on the NTP initiative to list *ISOPRENE* in the NTP's 9th Report on Carcinogens

IISRP submits these comments as follow-up to our previous letter sent to NTP in February 1998. We took issue with the conclusion concerning the level of evidence in NTP's review of the rat bioassay on isoprene, which was deemed to provide "clear evidence of carcinogenicity". On February 3, 1998, NTP gave notice that it intended to place isoprene on its list of carcinogens in its 9th report to be published in 1999.

This letter states our position that isoprene does not belong on the list of carcinogens as it does not meet criteria for listing. NTP criteria for listing a chemical include 1. A significant number of people residing within the US are exposed to the chemical, and 2. there is sufficient evidence of carcinogenicity from experimental studies.

Exposed Populations

While NTP does not define a "*significant number* of people residing in the US" exposed population, we have developed data on the isoprene industrial population in the US, and found that the number is far less than the 3700 number cited in the NTP's bioassay report. The total number of workers involved in the production of isoprene monomer and isoprene-based polymers is between 325 and 400. In addition, the bioassay report indicated that the majority of exposures were to workers who processed these polymers, and that most of this population was being subjected to isoprene residuals leaching from polymer matrices. Analysis of finished product data indicates that polyisoprene (the highest content of isoprene in any polymer) contains less than 0.1 ppm (100 ppb) of residual isoprene monomer. This number represents a concentration on a per weight basis, and the high affinity of the monomer for the polymer matrix suggests that air-borne levels in the polymer environment would be extremely low. Other isoprene copolymers (polymers derived from isoprene and one or more other monomers) are expected to have even lower levels of free isoprene monomer.

Finally, air-monitoring data for warehouses containing large stores of polyisoprene elastomer indicated undetectable levels of isoprene monomer. This suggests that potential exposures to workers from isoprene migration from polymers is negligible.

Evidence of Carcinogenicity

As part of the basis for including isoprene in the 9th List of Carcinogens is putative evidence for carcinogenicity from animal studies. While positive evidence of carcinogenicity exists for mice, the NTP bioassay for rats which is reported to have demonstrated "clear evidence of carcinogenicity" in male rats and "some evidence of carcinogenicity" in females provides scant evidence for carcinogenicity in a second species. There are substantial weaknesses and omissions in NTP's arguments that data from the study support criteria for the evidence of carcinogenicity.

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Focusing upon the male rat data, NTP has apparently over interpreted its own criteria as clear evidence for carcinogenicity. There was no tissue in treated rats for which there was a significant increase in malignant tumors. However, according to NTP's criteria, there must be "an increase in **combined** (emphasis added) benign and malignant tumors" as clear evidence. There was no increase in **combined**, which indicates NTP over interpreted its own criteria.

Another criterion which was verbally used to support "clear evidence" by NTP staff was that it is "well known" that benign tumors seen can progress to malignancies. But nowhere was it stated which tumors were considered likely to progress to malignant tumors, nor were citations provided to support the assertion. In fact, one of the tumor sites cited as important evidence for carcinogenicity was male mammary tissue, yet evidence that this tumor inevitably progresses to malignancies was not given. In addition, since the rat study assessed tumor yields in rats at 110 weeks of age (the majority of the rat's lifetime completed), certainly evidence of progression to malignancies from benign tumors would have been observed if this criterion was to be met. This, however, was not observed.

In summary, isoprene fails to meet criteria for inclusion in NTP's List of Carcinogens on two bases; exposed population in the US, and for sufficient evidence for carcinogenicity. Less than 400 workers are employed in monomer/polymer manufacturing, and less than 10% of those are exposed to isoprene levels in excess of 1 ppm. In addition, monomer residue analyses of isoprene polymer/copolymers demonstrate that individuals handling finished isoprene elastomers have negligible potential for toxicologically-significant exposures. This is supported by data collected for airborne levels of isoprene monomer in elastomer warehouses which indicated non-detectable levels (<0.008 ppm). Finally, due to NTP's failure to cite evidence of benign tumor progression to malignancies as well as its use of a newly-derived criterion which has not been either peer reviewed or published, NTP has not demonstrated that tumor data from the rat study support "clear evidence" for this species. In the absent of significant numbers of exposed individuals in the US plus lack of strong animal evidence, overall support for listing isoprene as a carcinogen is insufficient.

We appreciate the opportunity to provide additional comments on the proposed listing of isoprene.

Sincerely,

James L. McGraw

International Institute of Synthetic Rubber Producers, Inc.

James L. McGraw
Deputy Managing Director

JLM/rs

Isoprene Exposure Profile

Exposure Range PPM	3 Companies number in range >4 hour samples	% in Range
< 0.49	347	81.4
0.5-.99	42	9.9
1.0-1.99	12	2.8
2.0-2.99	8	1.9
3.0-3.99	3	0.7
4.0-4.99	2	0.4
5.0-9.99	6	1.4
>10.0	6	1.4

Number of workers	Both monomer and polymer production
Company A	100
Company B	60
Company C	165
Total	325

Job Titles

- Process Technician
- Lab Technician
- Isoprene Operator
- Product Loader
- Shipping/warehousing
- Stripper Operator
- Reactor Operator
- Polymer Finishing
- Supervisors
- Column Operator

Residual monomer in Finished Polymer

Company A	Not available
Company B	<100ppb
Company C	<100ppb